Implementation of the NICEATM-ICCVAM Five-Year Plan:
Advancing the Development, Validation, Acceptance, and Appropriate Use of Alternative Test Methods

S Fitzpatrick,[1] M Wind,[2] A Jacobs,[3] D Hattan,[4] J Kulpa-Eddy,[5] V Malshet,[3] M Mumtaz,[6] M Snyder,[7] D McCarley, [8] S Morefield,[9] C Sprankle,[9] D Allen,[9] W Stokes[8]

[1]U.S. Food and Drug Administration (FDA), Rockville, MD; [2]U.S. Consumer Product Safety Commission, Bethesda, MD; [3]U.S. FDA, Silver Spring, MD; [4]U.S. FDA, College Park, MD; [5]U.S. Department of Agriculture, Riverdale, MD; [6]Agency for Toxic Substances and Disease Registry, Chamblee, GA; [7]Office of the Director, National Institutes of Health, Bethesda, MD; [8]National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), Research Triangle Park, NC; [9]Integrated Laboratory Systems, Inc., Research Triangle Park, NC (contractor supporting NICEATM)

Abstract

Safety testing of chemicals, consumer products, and other substances is necessary to prevent injury and disease by identifying potential health hazards and ensuring proper hazard classification and labeling. ICCVAM's mission is to facilitate the development, validation, and regulatory acceptance of alternative safety test methods that protect human and animal health and the environment while reducing, refining, and replacing animal use. NICEATM and ICCVAM developed a Five-Year Plan in conjunction with its 15 member agencies that builds on the ICCVAM mission to achieve progress and to inform the public of their strategy. An overall goal of this plan is for ICCVAM to assume a greater leadership role in promoting research, development, translation, validation, and regulatory acceptance of alternative test methods. A working document has now been developed to describe how the strategies outlined in the Five-Year Plan are being implemented. Implementation activities address four key challenges: 1) identifying test method priorities and conducting and facilitating activities in these areas; 2) identifying and promoting new science and technology; 3) fostering regulatory acceptance and use of alternative test methods; and 4) developing partnerships. This plan is predicated on a proactive role for NICEATM and ICCVAM to identify and develop collaborations with experienced scientists that can bring state-of-the-art science to the forefront. This will require working closely with a broad range of stakeholders because ICCVAM, as an interagency committee, does not have resources to conduct research, development, and validation studies. Therefore, successful implementation will depend on these interactions both within and outside of ICCVAM agencies.
ILS staff supported by NIEHS contract N01-ES-35504.

Introduction: The NICEATM-ICCVAM Five-Year Plan

- The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is an interagency committee of the U.S. government.
  - ICCVAM is administered by the National Institute of Environmental Health Sciences (NIEHS) under the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).
- ICCVAM's mission is to facilitate development, validation, and regulatory acceptance of new, revised, and alternative test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.
- ICCVAM's vision is to play a leading role in fostering and promoting the development, validation, and regulatory acceptance of scientifically sound alternative test methods both within the Federal government and internationally.
- To ensure progress towards the ICCVAM mission and vision, NICEATM and ICCVAM developed the NICEATM-ICCVAM Five-Year Plan (ICCVAM 2008) in conjunction with Federal agency program offices. The Five-Year Plan maps out planned activities for the period 2008-2012.
- The NICEATM-ICCVAM Five-Year Plan identified four key challenges to be addressed:
  - Conduct and facilitate alternative test method activities in priority areas
  - Identify and promote research incorporating new technologies that will support the development of new test methods and approaches to reduce or eliminate the need for animals
  - Foster acceptance and appropriate use of alternative test methods
  - Develop partnerships and strengthen interactions with ICCVAM stakeholders
- NICEATM and ICCVAM have developed a working document that describes how they are implementing the strategies outlined in the Five-Year Plan. This poster summarizes that Implementation Plan and highlights progress made to date on achieving specific objectives. The full Implementation Plan may be found on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/docs/5yearplan.htm.

Challenge 1: Conduct and Facilitate Alternative Test Method Activities In Priority Areas

- ICCVAM priorities emphasize alternatives for those regulatory test methods that can use large numbers of animals and that can involve significant animal pain and distress. ICCVAM considers the following criteria when prioritizing test method nominations and submissions (ICCVAM 2003):
  - The potential impact that an alternative test method may have on reducing, refining, or replacing animals used in testing
  - The potential of a proposed test method to provide improved prediction of adverse health or environmental effects
  - The potential for an alternative test method to apply to regulatory testing required by multiple agencies
- Current ICCVAM priority areas include:
  - Ocular toxicity
  - Acute systemic toxicity
  - Dermal corrosivity and irritation
  - Biologics safety and potency
  - Immunotoxicity (dermal sensitization)
  - Endocrine disruption

  These priorities will likely evolve over time in response to new testing needs and advances in science and technology for specific types of toxicity.
- NICEATM and ICCVAM will identify critical knowledge and data gaps that need to be addressed in order to advance alternative methods for these priority areas.
- They will make recommendations to stakeholder organizations with resources to carry out the recommended research, development, and validation activities to address those gaps.
- When these activities identify promising new test methods, ICCVAM will evaluate the scientific validity of these methods for regulatory testing purposes and provide recommendations to regulatory agencies on demonstrated usefulness and limitations.

Biologics Testing

Objectives

- Recommend how *in vitro* test methods and humane endpoints can be used to reduce, refine, and eventually replace animal use for vaccine potency and efficacy testing while ensuring the protection of human and animal health
- Discuss how to promote the collection and submission of *in vitro* and *in vivo* test data in order to support the development and validation of such methods

Planned Activities

- Convene a scientific workshop to 1) evaluate the state of the science for possible alternatives and 2) the use of humane endpoints for *in vivo* potency tests
  - An "International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Vaccine Safety Testing: State of the Science and Future Directions" will be held September 14-16, 2010.
  - The workshop will take place at the William H. Natcher Conference Center on the main campus of the National Institutes of Health in Bethesda, MD.
  - More information, including agenda, abstract submission guidelines, and registration information for the workshop will be available on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/meetings/BiologicsWksp-2010/BiologicsWksp.htm.
- Evaluate *in vitro* potency tests for leptospirosis vaccines being developed by the U.S. Department of Agriculture
  - Formal submission to ICCVAM is anticipated in 2010

Preliminary Agenda of Workshop Sessions:

Session 1: Overview of Public Health Needs and Regulatory Requirements for Vaccine Testing

Session 2: Replacement Methods for Vaccine Potency Testing: Current State of the Science and Knowledge Gaps

Session 3: Refinement and Reduction Alternatives of Animal Use for Vaccine Potency Testing

Session 4: Vaccine Safety Testing: Post-licensing Refinement, Reduction and Replacement Alternative Methods and Strategies

Ocular Toxicity Testing

Objectives

- Identify alternative test methods that can accurately predict the hazards associated with substances that cause reversible eye damage.
- Identify testing batteries that could be used to increase the accuracy for predicting all ocular hazard categories.
- Promote the routine use of topical anesthetics and systemic analgesics and the inclusion of humane endpoints in current *in vivo* ocular toxicity tests

Planned Activities

- Evaluate *in vitro* approaches for assessing the ocular irritation potential of antimicrobial cleaning products
- Assess *in vitro* ocular toxicity test methods proposed for assessing reversible eye damage
- Review the routine use of topical anesthetics, systemic analgesics, and humane endpoints for reducing pain and distress during *in vivo* testing (see **Abstract 938**)
  - Draft recommendations reviewed by independent peer review panel May 2009 and by the Scientific Advisory Committee on Alternative Toxicological Methods in June 2009; final test method evaluation reports in preparation
- Evaluate the effect of specific protocol modifications on the relevance and reliability of the bovine corneal opacity and permeability test method
- Promote the evaluation of ocular histopathology for its potential to improve test method predictivity

Acute Systemic Toxicity Testing

Objectives

- Identify standardized procedures for collecting mechanistic information from acute oral toxicity testing to aid in developing batteries of predictive *in vitro* test methods
- Identify more objective endpoints that could be used to define evident toxicity in *in vivo* studies and enable early termination
- Explore opportunities to collaborate on efforts to develop an *in vitro* test strategy to completely replace *in vivo* testing of chemicals for acute toxicity
- Evaluate the up-and-down procedure and the fixed dose procedure to reduce animal use for acute dermal systemic toxicity and acute inhalation toxicity

Planned Activities

- Organize an international workshop to identify earlier, more humane endpoints and predictive batteries of *in vitro* test methods
  - A workshop entitled "Scientific Workshop on Acute Chemical Safety Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluations" was held in February 2008.
  - Conclusions from the workshop were presented at SOT in 2009 (Strickland et al. 2009).
- Promote the collection and submission of *in vitro* and *in vivo* toxicity test data to advance the development and validation of more predictive *in vitro* test methods and earlier, more humane endpoints for acute systemic toxicity testing
- Participate on an international study on a human hepatic biotransformation enzyme induction assay using HepaRG cells and cryopreserved human hepatocytes

Key findings of the February 2008 workshop:

- Objective data to help identify mechanisms of toxicity and death should be routinely collected during animal studies required for regulatory testing.
- *In vivo* measurements should also be collected to aid in the identification of predictive earlier endpoints of severe toxicity, and to establish objective parameters for evident toxicity.
- *In vivo* mechanistic data should be used to guide the selection of *in vitro* tests for high throughput screening and other research initiatives attempting to identify *in vivo* toxicity pathways.
- Significant R&D efforts will be needed to develop sufficiently predictive *in vitro* models of acute systemic toxicity.

Dermal Toxicity Testing

Objectives

- Determine the usefulness and limitations of *in vitro* skin model systems for skin irritation testing
- Determine how corrosive substances that have produced false negative results in *in vitro* corrosivity test methods will act in the *in vitro* dermal irritation test method protocols

Planned Activities

- Assist in the development of an Organisation of Economic Co-operation and Development (OECD) test guideline for human skin model systems for skin irritation testing
  - Final draft test guideline forwarded to OECD in February 2010
- Conduct a study to evaluate potential false negative corrosive chemicals in proposed *in vitro* dermal irritation assays
  - Study is currently ongoing

Dermal Sensitization Testing

Objectives

- Identify adequately validated test methods that can detect potential skin sensitizers without the requirement for radioactivity
- Identify ways to reduce the number of animals required for skin sensitization testing
- Collect and review current murine local lymph node assay (LLNA) data to determine whether the applicability domain of the LLNA can be expanded
- Explore opportunities to collaborate on developing *in vitro* testing strategies to replace animal tests currently used to characterize potential sensitizers

Planned Activities

- Develop an updated LLNA test method protocol that reduces animal use
  - Final ICCVAM recommendations on an updated LLNA protocol that reduces animal use by an additional 20% were forwarded to U.S. Federal agencies in September 2009; responses from agencies are due March 22, 2010 (ICCVAM 2009a)
- Evaluate the validation status of:
  - The LLNA as a stand-alone assay for potency determination for classification purposes (see **Abstract 1807**)
  - The LLNA for testing pesticide formulations and other products (see **Abstract 1789**)
    - ICCVAM scientists prepared a revision of OECD Test Guideline 429, currently under review, that reflects the updated applicability domain
  - Modified LLNA protocols that do not use radioactivity
    - ICCVAM scientists prepared new OECD draft test guidelines for the nonradioactive LLNA methods, which are currently under OECD review
  - The reduced LLNA test method, which can reduce animal use requirements for the LLNA by 40%
    - Final ICCVAM recommendations on the reduced LLNA were forwarded to U.S. Federal agencies in September 2009; responses from agencies are due March 22, 2010 (ICCVAM 2009b)
    - Incorporated into updated OECD Test Guideline 429
- Develop test method performance standards for the LLNA that could be used to quickly and efficiently evaluate modified versions of the LLNA
  - Final ICCVAM-recommended performance standards for the LLNA were forwarded to U.S. Federal agencies in September 2009; responses from agencies are due March 22, 2010 (ICCVAM 2009a)
  - Incorporated into updated OECD Test Guideline 429

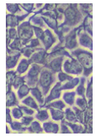
Endocrine Disruptors Testing

Objectives

- Complete an international study to evaluate the LUMI-CELL® estrogen receptor transcriptional activation assay protocols for both the detection of estrogenic and anti-estrogenic activity
- Provide support for the validation of the Certichem, Inc., MCF-7 Cell Proliferation Assay protocols for both the detection of estrogenic and anti-estrogenic activity
- Increase involvement in OECD test guideline activities related to endocrine disruptors.

Planned Activities

- Standardize and optimize the protocols for the LUMI-CELL® ER assay and evaluate test method reliability.
  - The laboratory testing phase of the validation study is complete, with an upcoming ICCVAM expert peer review panel meeting (see **Abstract 101**).
- Use the results from the LUMI-CELL® validation study to develop a high quality *in vitro* database and performance standards for estrogen receptor transcriptional activation assays
- Facilitate the interlaboratory validation of the Certichem, Inc., MCF-7 Cell Proliferation Assay



Acknowledgements

This poster was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences. ILS staff are supported by NIEHS contract N01-ES 35504. The views expressed on this poster do not necessarily represent the official positions of any Federal agency. Since the poster was written as part of the official duties of the authors, it can be freely copied.

Challenge 2: Incorporate New Science and Technology

- Relevant new technologies need to be identified and utilized to support the future development of new test methods and approaches that reduce or eliminate the need for animals
  - Current efforts focus on high throughput screening initiatives and nanomaterials testing
- NICEATM and ICCVAM have surveyed and are working with Federal agencies and other stakeholders to link research activities to the development and validation of alternative test methods that may be used in regulatory testing.
  - An ICCVAM Research and Development Working Group (RDWG) was established to coordinate activities relevant to incorporating new science and technology as outlined in the Five-Year Plan.
  - Recent RDWG meetings have included discussions with scientists from:
    - Environmental Protection Agency (EPA) Center for Computational Toxicology
    - EPA National Health and Environmental Effects Research Laboratory
    - NIEHS Division of Extramural Research and Training
    - NTP Biomolecular Screening Branch
    - OECD Working Party on Manufactured Nanomaterials
  - The RDWG includes scientists that are integrally involved in Agency research programs in order to help identify promising test methods for referral to appropriate ICCVAM working groups for evaluations or other activities

High Throughput Screening

Objectives

- Facilitate the review of defined high throughput screening approaches
- Assist in the identification of assays and endpoints that are relevant for alternative test methods that have already been adopted.

Planned Activities

- Monitor progress of an interagency collaboration between NIEHS/NTP, EPA, and the National Institutes of Health Chemical Genomics Center (i.e., "Tox 21" [Schmidt 2009])
  - Evaluate the predictivity of *in vitro* methods included in Tox 21, particularly as they relate to the ICCVAM priority endpoints (ocular toxicity, acute systemic toxicity, dermal, corrosivity and irritation, biologics safety and potency, immunotoxicity, endocrine disruption)
  - Identify candidate methods and approaches generated through Tox 21 with potential applicability to regulatory testing.
    - Facilitate test method standardization and validation
    - Forward recommendations on usefulness and limitations of identified methods to appropriate agencies
- Nominate substances for inclusion in future Tox 21 testing such as:
  - Substances identified as reference compounds in previous NICEATM-ICCVAM evaluations
    - NICEATM recently forwarded a list of over 700 reference substances for inclusion in the next phase of Tox 21 testing
  - Additional substances that have been tested in various alternative test methods, in the standard *in vivo* toxicity tests, or in humans.

ICCVAM Five-Year Plan Implementation Subcommittee/Research and Development Working Group

★*Five-Year Plan Implementation Subcommittee*
◆*Research and Development Working Group*

Agency for Toxic Substances and Disease Registry
◆*Bruce Fowler, Ph.D.*
★*Moiz Mumtaz, Ph.D.*

Consumer Product Safety Commission
★*Marilyn Wind, Ph.D.*

Department of Agriculture
★*Jodie Kulpa-Eddy, D.V.M.*

Department of Defense
★*Leonard Smith, Ph.D.*

Environmental Protection Agency
◆*John Fowle, Ph.D., DABT*

Food and Drug Administration
Office of the Commissioner
★*Suzanne Fitzpatrick, Ph.D., DABT (Subcommittee Chair)*
Center for Drug Evaluation and Research
★*David Hattan, Ph.D.*
★*Abigail Jacobs, Ph.D.*
Center for Devices and Radiological Health
★*Vasant G. Malshet, Ph.D., DABT*
Center for Biologics Evaluation and Research
◆*Richard McFarland, Ph.D., M.D.*
National Center for Toxicological Research
◆*Donna Mendrick, Ph.D.*

National Cancer Institute
◆*Myrtle Davis-Millin, D.V.M., Ph.D.*

National Institute of Environmental Health Sciences
◆*Jerrold Heindel, Ph.D.*
★*Deborah McCarley*
★*William Stokes, D.V.M., DACLAM*
★*Raymond Tice, Ph.D.*

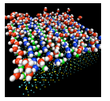
National Institutes of Health
★*Margaret Snyder, Ph.D.*
◆*Christine Kelley, Ph.D.*

Japanese Center for the Validation of Alternative Methods - Liaison
◆*Hajime Kojima, Ph.D.*

Nanomaterials Testing

Objectives

- Work with stakeholders to identify test methods that are considered to be most appropriate for nanomaterials
- Foster the development and evaluation of alternative methods for nanomaterials testing
- Identify the current and planned activities within or supported by ICCVAM agencies that are relevant to nanomaterials testing and the use of alternative test methods



Planned Activities

- Assess the state of the science to determine if developing a scientific workshop to evaluate possible alternatives is warranted
- Develop a one-day symposium presenting planned activities within ICCVAM agencies that are relevant to nanomaterials testing and the use of alternative methods
- Provide input on OECD activities relevant to alternative test methods intended for safety testing of nanomaterials

Challenge 3: Foster Acceptance and Appropriate Use of Alternative Test Methods

- NICEATM and ICCVAM will work to promote the use of accepted alternative test methods by broadly communicating the outcomes of ICCVAM review activities.
- NICEATM and ICCVAM will work to inform the scientific community, including Institutional Animal Care and Use Committees, of new alternatives that should be considered for use prior to testing in animals.

Development of Internet Resources

Objectives

- Ensure that the NICEATM-ICCVAM website provides ready access to the latest information on validation processes and the current status of alternative test method evaluation activities
- Provide access to publicly available reference test method databases for use in the development and validation of alternative test methods
- Promote active communication and outreach efforts with both government and non-government stakeholders

Planned Activities

- Work with ICCVAM agencies to create agency-specific websites dedicated to their activities in alternative test methods research, development, translation, and validation
- Develop lists of frequently asked questions for the NICEATM-ICCVAM website
  - General list is available at http://iccvam.niehs.nih.gov/about/ni_QA.htm; additional, more specific lists under development
- Create a summary on the NICEATM-ICCVAM website of all test methods that have been reviewed or that are currently undergoing review
  - Available at http://iccvam.niehs.nih.gov/methods/milestones.htm

Posters at SOT Describing Activities Supporting the NICEATM-ICCVAM Five-Year Plan

For more information on current NICEATM-ICCVAM activities that support the objectives of the Five-Year Plan, please visit the following posters:

Abstract Number	Title	Exhibit Time	Poster Board Number
101	Testing of Coded Test Substances in the NICEATM/ECVAM/JaCVAM LUMI-CELL ER® STTA Multi-phased International Validation Study	Monday, March 8, 9:00-12:30	117
938	ICCVAM Recommendations for the Routine Use of Anesthetics, Analgesics, and Humane Endpoints to Refine Ocular Toxicity Testing.	Tuesday, March 9, 9:00-12:30	642
1789	ICCVAM Recommendations for Use of the LLNA for Evaluating the Allergic Contact Dermatitis Potential of Pesticide Formulations and Other Products	Wednesday, March 10 1:00-4:30	233
1807	Using of the Murine Local Lymph Node Assay to Categorize Strong Skin Sensitizers	Wednesday, March 10 1:00-4:30	303
1810A	Establishment of the International Cooperation on Alternative Test Methods (ICATM) and Its Role in the Validation and Regulatory Acceptance of Globally Harmonized Safety Assessment Methods	Wednesday, March 10 1:00-4:30	307

Challenge #4: Developing Partnerships and Strengthening Interactions with ICCVAM Stakeholders

Objectives

- Be proactive in identifying research needs and promising methods that should be priorities for further development, translation, validation, or ICCVAM evaluation
- Foster interagency collaboration among Federal research and regulatory agencies, including opportunities for test method validation activities.
- Strengthen international relationships with appropriate organizations to foster the validation and evaluation of alternative test methods
- Foster international collaboration by including experts from the international scientific community on expert panels and workshops

Planned Activities

- Collaborate with international government and non-governmental organizations, where appropriate, to co-sponsor workshops to identify high priority activities necessary to advance and characterize the usefulness of alternative methods.
  - Workshop on vaccine potency and safety to be held September14-16, 2010
  - Workshop on appropriate and effective use of validated test methods planned for Fall 2010
- Facilitate the international adoption of valid alternative test methods by providing standardized protocols that can be considered for adoption by international organizations
  - ICCVAM and NICEATM were the leads on two new test guidelines for identification of ocular corrosives and severe irritants which were accepted in 2009 by OECD (for use of the bovine corneal opacity and permeability and isolated chicken eye test methods).
  - ICCVAM and NICEATM prepared, commented on, or otherwise contributed to the development of 23 new OECD test guidelines, revisions of existing test guidelines, and guidance documents in 2008 and 2009.
- Work with other national and international validation organizations to promote ICCVAM's validation and acceptance criteria
  - ICCVAM signed a Memorandum of Cooperation that established an International Cooperation on Alternative Test Methods to expand and strengthen cooperation, collaboration, and communications among national validation organizations (see **Abstract 1810A**)
  - NICEATM and ICCVAM provided liaison members to international validation study management teams.
- Participate in the development of performance standards for international test guidelines
  - Internationally harmonized performance standards for the LLNA
- Increase participation of NICEATM and ICCVAM scientists in U.S. delegations to OECD test guideline meetings, expert consultations, and workshops.
  - NICEATM and ICCVAM co-hosted an OECD expert consultation meeting which considered revised and new test guidelines for the LLNA.
  - NICEATM and ICCVAM representatives participated in expert reviews of OECD draft test guidelines for dermal and ocular test methods.
- Continue to encourage international participation in relevant NICEATM and ICCVAM-sponsored workshops, peer reviews, and other scientific activities
- Engage interested stakeholders in assessing how to efficiently meet Federal peer review requirements, and seek input on ways to streamline processes that will not compromise transparency, scientific rigor, or the opportunity for stakeholder participation.

References

ICCVAM. 2003. ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods. NIH Publication 03-4508. Research Triangle Park, NC: National Institute of Environmental Health Sciences. Available: http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.pdf.

ICCVAM. 2008. NICEATM-ICCVAM Five-Year Plan (2008-2012): A Plan to Advance Alternative Test Methods of High Scientific Quality to Protect and Advance the Health of People, Animals and the Environment. NIH Publication 08-6410. Research Triangle Park, NC: National Institute of Environmental Health Sciences. Available: http://iccvam.niehs.nih.gov/docs/5yearplan.htm

ICCVAM. 2009a. Recommended Performance Standards: Murine Local Lymph Node Assay. NIH Publication 09-7357. Research Triangle Park, NC: National Institute of Environmental Health Sciences. Available: http://iccvam.niehs.nih.gov/methods/immunotox/PerfStds/llna-ps.htm.

ICCVAM. 2009b. ICCVAM Test Method Evaluation Report. The Reduced Murine Local Lymph Node Assay: An Alternative Test Method Using Fewer Animals to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products. NIH Publication 09-6439. Research Triangle Park, NC: National Institute of Environmental Health Sciences. Available: http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-LD/TMER.htm

Schmidt C. 2009. TOX 21: New Dimensions of Toxicity Testing. Environ Health Perspect 117:A348-A353

Strickland J, Paris M, Allen D, Tice R, Kojima H, Prieto P, Wind M, Stokes W. 2009. ICCVAM/NICEATM/ECVAM/JaCVAM scientific workshop on acute chemical safety testing: advancing in vitro approaches and humane endpoints for acute systemic toxicity evaluations [Abstract]. Presented at the 48th Annual Meeting of the Society of Toxicology. Toxicologist 108. Available: http://iccvam.niehs.nih.gov/meetings/SOT09/Strickland.pdf.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIEHS National Institute of Environmental Health Sciences

NTP